Pulmonary talc granulomas, pulmonary fibrosis, and pulmonary hypertension resulting from intravenous injection of talc-containing drugs intended for oral use

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Talcosis or talc pneumoconiosis is an uncommon form of pulmonary dust disease first recognized over 100 years ago. Talcosis may follow inhalation of relatively low concentrations of talc dust over a long period or exposure to very high concentrations of the dust over a short time (1, 2). In an infant, death occurred within 20 hours of accidental inhalation of talcum powder containing approximately 93% talc (3). Baby powder, consisting mainly of talc powder, is insoluble and, if inhaled in large amounts, dries the tracheobronchial mucous membrane and prevents normal ciliary function. The small air passages then fill with retained mucus.

Talc, or hydrated magnesium silicate, is formed during the breakdown and weathering of serpentine, tremolite, and anthrophyllite rock (1). The fibrogenic properties of talc are attributed to these impurities, especially anthrophyllite and tremolite, which are members of the asbestos group of minerals.

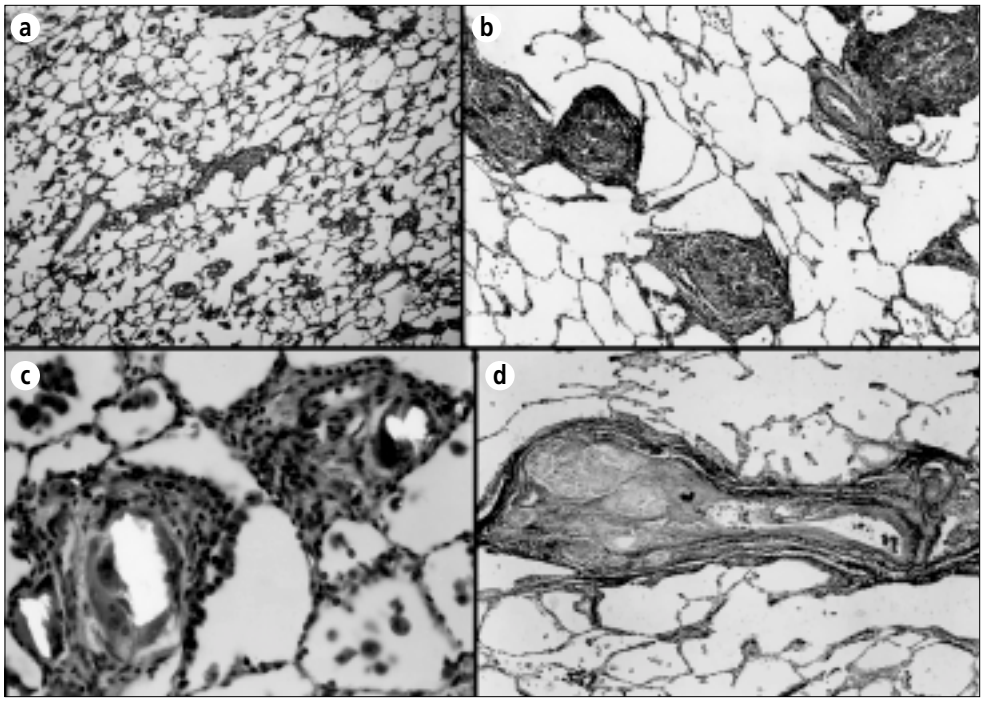

Figure 1. Histologic sections from the excised left lower lobe of the lung of a 23-year-old man who had been an intravenous drug addict (heroin, methadone, and methylphenidate tablets) since age 18. Interstitial talc granulomas are shown in **(a), (b),** and **(c)** at progressively higher magnifications. The refractile talc is best seen in **(c).** Intra-arterial granuloma, shown in **(d),** is an unusual occurrence in this patient. **(a, b, c)** Hematoxylin and eosin stains; **(d)** elastic van Gieson stain. Original magnification: **(a)** ×16; **(b)** ×54; **(c)** ×160, and **(d)** ×80. Reprinted from reference 4, copyright 1976, with permission from Excerpta Medica Inc.

Talc pneumoconiosis has been described in persons in several occupations, including talc mining and milling; manufacture of rubber cable and tires, accumulator plates, cosmetics, soaps, paints, and textiles; and sailing, since sailors dust life rafts with talc.

A new form of talc pulmonary disease, described initially in the 1960s, occurs in intravenous drug addicts who also inject tablets intended for oral use (4–10). Because most tablets (including phenmetrazine and methylphenidate) contain talc, which is used to hold the components of the medication together in tablet form, this practice can cause arterial obstruction by this foreign material. When these talc-containing drugs are injected into blood vessels rather than swallowed, foreign-body granulomatous reactions occur *(Figure 1)*. Injection of these talc-containing drugs into a peripheral artery may cause ischemic necrosis of portions of the distal extremities or another organ (4). The more common practice of injecting these drugs into peripheral veins results in foreign-body granulomas in the lungs.

The exact percentage of addicts who follow this practice is uncertain (4). As shown in *Figure 2*, however, it is probably about 1% of nonalcohol drug addicts. Among intravenous drug addicts, all appear to inject opiates and probably none inject only tablets. It is probable that only a small percentage of opiate addicts frequently inject tablets. Thus, of all the intravenous drug users, pulmonary talc granulomas develop in only about 5%, i.e., those

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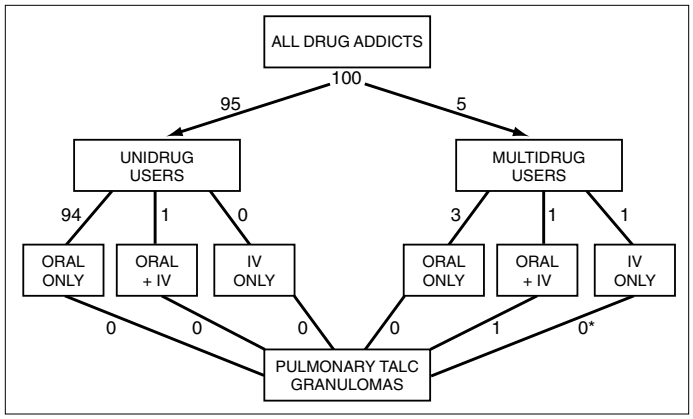

Figure 2. Among all persons who abuse drugs, those who use only one drug constitute the great majority, and those who abuse many drugs, the minority. Virtually all intravenous drug abusers appear to fall into the multidrug group. Talc granulomas form only in multidrug users because the intravenous injectors of tablets intended for oral use also usually use intravenous opiates and/or ingest drugs orally as well. Reprinted from reference 4, copyright 1976, with permission from Excerpta Medica Inc.

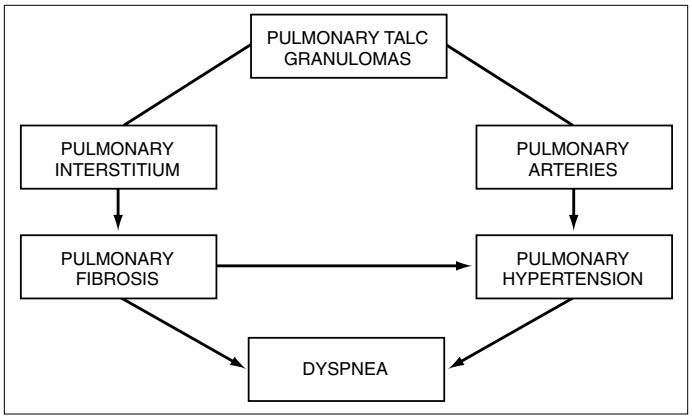

Figure 3. The effect of pulmonary talc granulomas located in pulmonary interstitium or in lumens of pulmonary arteries. Reprinted from reference 4, copyright 1976, with permission from Excerpta Medica Inc.

who also inject oral tablets. Pulmonary talc granulomas do not result from intravenous injection of opiates alone, because these drugs are diluted by maltose, lactose, and quinine, called "fillers," all of which are readily soluble.

Of reported intravenous drug addicts with pulmonary talc granulomas confirmed morphologically by lung biopsy or necropsy, virtually all had repeatedly injected medications intended for oral use. Six different medications have been reported to be associated with talc granulomas in addicts: methylphenidate (Ritalin), methadone, tripelennamine (Pyribenzamine), propoxyphene (Darvon), phenmetrazine (Preludin), and amphetamines; all contain talc. The foreign material present in the granulomas is morphologically consistent with talc, and in several reported patients, x-ray diffraction studies positively identified the material as talc (1). Additionally, when various components of drugs associated with granulomas are injected into experimental animals, only talc produces granulomas. Thus, talc, long known to cause foreign-body granulomatous reactions when applied to serosal surfaces and similar granulomatous reactions in the lungs when inhaled over prolonged periods, also produces foreign-body granulomas when injected intravenously as part of a dissolved oral medication.

The reaction to talc, however, is variable *(Figure 3)*. In some patients, widespread granulomas develop in the interstitium of the lung but relatively few in the pulmonary arteries. In other patients, this interstitial reaction may eventually lead to interstitial pulmonary fibrosis and to clinical evidence of restrictive lung disease. Other patients, after intravenous injection of oral medications, have talc granulomas predominantly in the lumens of small pulmonary arteries rather than in the interstitium. The result in these patients is pulmonary arterial hypertension rather than interstitial pulmonary disease. The pulmonary hypertension causes medial hypertrophy of the pulmonary arteries, often intimal fibrous thickening, and occasionally plexiform lesions in the lungs. The occurrence of plexiform lesions indicates that the pulmonary hypertension is irreversible (11).

Why the pulmonary talc granulomas are located predominantly in the interstitium in some patients and predominantly in the lumens of the pulmonary arteries in others is unclear. The total amount of injected talc must be important, but quantity may not be the only factor. It is unlikely that the type of tablet injected plays an important role, because a number of reported patients with severe pulmonary hypertension and predominantly intravascular granulomas injected different talc-containing drugs. Conceivably, there are differences in the talc itself, or possibly people react differently to injections of identical talc.

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